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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/477,097 06/07/95 LIVINGSTON

P 43016-B/JPW/

EXAMINER

HM12/0619

JOHN P WHITE
COOPER & DUNHAM
1185 AVENUE OF THE AMERICAS
NEW YORK NY 10036

DUFFY, P

ART UNIT

PAPER NUMBER

1645

25

DATE MAILED:

06/19/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/477,097

Applicant(s)

Livingston et al.

Examiner

Duffy

Group Art Unit

1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☒ Responsive to communication(s) filed on 4-5-00
- ☒ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 78-99 is/are pending in the application.
- Of the above claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 78-99 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the international Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Other _____

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Response to Amendment

1. The amendment filed 4-5-00 has been entered into the record. Claims 78-99 are pending and under examination.
2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.
3. Any rejections not reiterated herein are withdrawn based on applicants amendments.

Objections / Rejections Maintained

Specification

4. The prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/10/96 (see Paper No. 9).

Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. Until applicants submit a proper Figure said objection is maintained.

Double Patenting

5. New claims 78-99 are provisionally rejected under the judicially created doctrine of obviousness-type, double patenting as being unpatentable over the claims 78-100 of copending Application No. 08/475,784 for reasons already made of record in Paper No. 23, mailed 10-5-99.

Applicants' assert that the added new claims in the copending application obviate the obvious type double patenting. Applicants' assertion is not persuasive since the claims of the instant application encompass conjugating the ceramide portion of GM2 via a variety of linkages to keyhole limpet hemocyanin (KLH) as recited the claims in copending application. Applicants

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amendments are insufficient to remove the rejection. Even if applicants limited the '784 application to remove GD2, it is noted that the conjugation of other gangliosides would be obvious over the each other because they all have similar base structure and are derived from GM3 as indicated by Ritter et al (Cancer Biology, 1991) of record.

6. New claims 79-99 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44 and 46-56 of copending Application No. 08/477,147 for reasons already made of record in Paper No. 23, mailed 10-5-99.

Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the prior Office Actions. Applicants' amendments are insufficient to overcome the double patenting rejection in regard to 08/477,147.

7. New claims 79-99 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 97-118 of copending Application Nos. 08/196,154 for reasons already made of record in Paper No. 23, mailed 10-5-99.

The instantly claimed compositions drawn to specific species of gangliosides conjugated to KLH by a specific C-4 bond (see claim 79) anticipate the claims of 08/196,154. Applicants' assertion that the amendment to the claims obviates the double patenting rejection is not persuasive.

8. New claims 93-99 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons for reasons made of record in Paper No. 16, mailed 7-11-97.

Applicants' arguments have been carefully considered but are not persuasive. Applicants' argue that the conjugate vaccine of the invention prevents outgrowth of

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micrometastases and prevents cancer *per se* (Zhang et al, Cancer Research 58:2844-2849, 1998). This is not persuasive, the claims are not drawn to preventing outgrowth of micrometastases and the conjugate used in the paper is GD2-KLH (10 ug of GD2 conjugated to 60 ug KLH, wherein the conjugation of GD2 to KLH was achieved by conversion of the GD2 ceramide double bond to aldehyde by ozonolysis and attachment to KLH by reductive amination in the presence of cyanoborohydride) plus 10 ug QS-21. Thus, the conjugate of the claims is not that which has been demonstrated by the art prevents outgrowth of micrometastases, nor does the method provide for the method of the paper (multiple doses administered by a specific route. Moreover, the article specifically teach that the vaccine "... should be used exclusively in the adjuvant setting, where circulating tumor cells and micrometastases are the primary targets (page 2844, last line of abstract)." The evidence of the paper targeted circulating cells specific type of tumor cell (lymphoma) which was administered intravenously and micrometastases thereof from circulation, which is clearly not representative of cancers or relapses as instantly claimed. Moreover, Figure 1, demonstrates that administration of the GD2-KLH, QS-21 vaccine at days -21, -14 and -7 does not prevent cancer as demonstrated by the death of some of the experimental group after experimental intravenous challenge of lymphoma cells (see Figure 1, Experiments 3 and 6B). At page 2845, column 2, second and third paragraph, Zhang et al teach that the vaccine prolonged survival, but in the discussion of experiment 6, only 4 out of 6 vaccinated mice remained disease free at the latest time point measured. Moreover, Zhang et al admit that the alleged protection in Experiment 7 of Figure 1, was "not statistically significant" and moreover this experiment is not directly comparable with the other experiments because the tumor burden administered intravenously was substantially reduced. Clearly the vaccine when administered prior to the cancer does not prevent as claimed or as argued by applicants.

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Additionally, prevention of relapse as claimed has not been demonstrated nor specifically addressed by this paper and Zhang et al admits that "If antibodies of sufficient titer and potency to eliminate circulating cancer cells and micrometastases could be maintained in cancer patients as well, even metastatic cancer would have quite a different implication. With continuing showers of metastases no longer possible, aggressive treatment of primary and metastatic sites might result in long term control." Relapsing of cancer is quite different than elimination of micrometastases and the paper only addresses circulating syngeneic tumor lymphoma cells and micrometastases (see page 2848, column 1, last paragraph) not primary cancer. Zhang et al do not address primary cancer and the experimental protocols set forth therein do not address prevention of primary cancer as is claimed for prevention of relapse of cancer. Reduction of circulating lymphoma cells and reduction in micrometastases is not commensurate in scope with prevention of cancer or prevention of a relapse of cancer.

The rejection is maintained.

9. Claims 53-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants point to a variety of pages to support the invention claiming "altered ceramide portion". As previously set forth, Applicants' disclosure provides for a single means of conjugating the ceramide of gangliosides to KLH, by means of the passage at page 32, lines 13-18 which provide for a *specific coupling procedure at the C-4 carbon of the sphingosine moiety of the ceramide to the ε-aminolysyl group of a proteins* (ozonolysis, production of a functional aldehyde group and coupling to an ε-aminolysyl group on a protein by reductive amination). The

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passage at page 12, lines 22-26 in combination with the passage at page 32, lines 13-18 does not support a broad coupling to any generic portion of the ceramide backbone of the ganglioside, by any generic means by cleavage of any double bond (i.e. C=O) and coupling by any linkage process or any generic alteration. The specification does not support by way of written description, convey that applicants had at the time of filing broadly contemplated any means of altering the ceramide, any means of coupling to any portion of the ceramide or broadly any alteration of the ceramide portion of the ganglioside, a concept that is now broadly claimed. Applicants' specification provide for a single means as set forth above. No generic contemplation of conjugation was contemplated nor generic alterations of the ceramide portion were contemplated at the time of filing. Applicants' were still clearly not in possession of that which is now broadly claimed. Correction is required. Applicants' amendments are insufficient to obviate this rejection.

10. Claims 78-94 and 96-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) is maintained for reasons made of record for claims 53-66 and 68-77 in Paper No. 23, mailed 10-5-99 and reiterated below.

Livingston et al (Cancer Research) teach a composition administered to melanoma patients for stimulation the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (page 7046-7048). Livingston et al teach that the composition for

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treatment is administered at a concentrations of 100, 200, or 300 ug with an adjuvant, Bacillus-Calmette-Geurin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, (p 7046, column 1, paragraph 3, and paragraph bridging p 7046-47). Livingston et al teach that melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (pate 7047, paragraph bridging columns 1-2). Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2). Livingston et al differ by not teaching the conjugation of the GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on Keyhole Limpet Hemocyanin (KLH) in a composition and using this composition for treatment.

Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). Ritter et al teaches discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose or the amino group bearing glass beads.

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Ritter et al (1990) teach that GD3 lactone is more immunogenic than GD3.

Livingston et al (U.S. Patent No. 5, 102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28).

Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose or the amino group bearing glass beads.

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Livingston et al by conjugating the GM-2 to KLH by covalently coupling GM2 to KLH by substituting GM2 for the globoside and KLH for the aminoethyl agarose to produce a GM-2-KLH conjugate by means of the olefinic bond of the

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sphingosine moiety of the GM2 (i.e. the instant ceramide double bond) and the ϵ -aminolysyl groups present in the KLH protein using the method of Liane et al and add QS-21 as an adjuvant to the GM-2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages by Ritter et al (1991) and adding the QS-21 would be advantageous because it provides for a higher antibody response than the commonly used adjuvant used by Kensil et al and QS-21 provides the advantages that it is not toxic to animals as is taught by Marciani et al. It also would have been *prima facie* obvious to use doses of between 10 and 80 ug of QS-21 in the composition and optimize the dose accordingly because the immune response with QS-21 plateaus at doses between 10-80 ug and optimization of the weight ratio of the components of the composition to provide an optimal response is well within the ordinary skill in the art and use the composition as modified supra for treatment of melanoma as taught by Livingston et al (Cancer Research) . It also would have been *prima facie* obvious to one of ordinary skill in the art to substitute any one of GM3, GD2, GD3, or O-acetyl GD3 for the GM2 ganglioside in the composition and method as combined supra because they are all prominent cell-membrane components of melanomas as taught by Livingston et al (U.S. Patent No. 5,102,663) and one of ordinary skill in the art would react with the melanoma cells. It would have also been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GD3 lactone for the GM2 ganglioside in the composition because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990) and would be expected to product an enhanced antibody response as compared to GD3. Optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is will within the skill of the ordinary artisan.

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One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the ϵ -aminolysyl groups of carrier proteins for enhance immunogenicity is routine in the art and Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies.

Applicants' arguments have been carefully considered but are not persuasive. Applicants' contend that the references neither alone nor in combination teach the claimed invention of conjugation of the ganglioside derivative through a ceramide derived carbon. This is not persuasive, the conjugation procedure as combined provides for the identical procedure as Applicants' coupling procedure. Moreover, the combination provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies. Applicants' have neither pointed distinguishing features of applicants invention nor provided any scientific evidence or rationale which would indicate that the conjugation procedure as combined by the prior art would not arrived at the claimed product and methods. Applicants arguments are not persuasive and the rejection stands across the new claims.

11. New claim 95 is rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem, 79(6):1253-1261, 1976) as applied to claims 78-94 and 96-99 above and further in view of Irie et al. (U.S. Patent Nol 4,557,931) is maintained for reasons made of record for claim 67, in Paper No. 23, mailed 10-5-99.

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The teachings of Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al, and Marciani et al., and Uemura et al (J Biochem, 79(6):1253-1261, 1976) are set forth *supra*. The combination differs by not teaching the administration of the composition for treating cancer of epithelial origin.

Irie et al teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the GM-2-KLH conjugate/ QS-21 composition or other ganglioside conjugate/QS-21 composition as combined *supra* to patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e. breast carcinomas) because the ganglioside GM-2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

Applicants' arguments have been carefully considered but are not persuasive. Applicants' contend that the references neither alone nor in combination teach the claimed invention of conjugation of the ganglioside derivative through a ceramide derived carbon. This is not persuasive, the conjugation procedure as combined provides for the identical procedure as Applicants' coupling procedure. Moreover, the combination provides a reasonable expectation of success as demonstrated by Uemura et al which demonstrates the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies. Applicants' have neither pointed distinguishing features of applicants invention nor provided any scientific evidence or rationale which would indicate that the conjugation procedure as combined by the

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prior art would not arrived at the claimed product and methods. Applicants arguments are not persuasive and the rejection stands across the new claims.

Status of Claims

12. All claims stand rejected.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire **THREE MONTHS** from the date of this action. In the event a first response is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than **SIX MONTHS** from the date of this final action.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

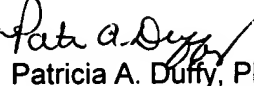
Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to

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reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
June 18, 2000


Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600